CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc.

Investigational Product: MSB0010718C

Clinical Study Report Synopsis: Protocol B9991009

Protocol Title: A Phase 3, Multicenter, Randomized, Open-Label Study of Avelumab (MSB0010718C) Alone or in Combination With Pegylated Liposomal Doxorubicin Versus Pegylated Liposomal Doxorubicin Alone in Patients With Platinum Resistant/Refractory Ovarian Cancer

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 21 December 2015

Primary Completion Date: 19 September 2018

Report Date: 30 April 2019

Previous Report Date(s): Not applicable

Phase of Development: Phase 3

Primary and Secondary Study Objectives and Endpoints: The primary and secondary objectives and endpoints are outlined in Table 1.

CLINICAL STUDY REPORT SYNOPSIS

Table 1. Primary and Secondary Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Efficacy	• To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging OS in patients with platinum-resistant/platinum-refractory ovarian cancer.	• OS
	• To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging PFS in patients with platinum-resistant/platinum-refractory ovarian cancer.	• PFS as determined by BICR according to RECIST version 1.1
Secondary		
Efficacy	• To evaluate anti-tumor activity of avelumab given alone or in combination with PLD versus PLD alone in ovarian cancer patients.	• PFS as determined by investigator according to RECIST version 1.1 • OR, DR, and DC as determined by BICR and Investigator (as assessed by RECIST version 1.1)
Safety	• To evaluate the overall safety profile of avelumab alone or in combination with PLD versus PLD alone in ovarian cancer patients.	• AEs (as graded by NCI CTCAE version 4.03); laboratory abnormalities (as graded by NCI CTCAE version 4.03); vital signs (BP and pulse rate); ECGs, ECHO or MUGA scans
PK (None Reported)	• To characterize the PK of doxorubicin (PLD samples) and avelumab when administered in combination, and to assess the effect of avelumab on the PK of doxorubicin (PLD sample) and the effect of PLD on PK of avelumab.	• PK parameters, including C_{trough} and C_{max} for avelumab, C_{max}, V_d, CL, and AUC for doxorubicin (PLD samples)
Immunogenicity (None Reported)	• To assess the immunogenicity of avelumab.	• Incidence of ADA and nAb against avelumab
Biomarker	• To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab or PLD in combination with avelumab in pre-treatment tumor tissue, that may aid in the identification of patient subpopulations most likely to benefit from treatment.	• Candidate predictive biomarkers in tumor tissue including, but not limited to, PD-L1 expression and tumor infiltrating CD8+ T lymphocytes as assessed by IHC
PRO	• To compare the effect of avelumab alone or in combination with PLD versus PLD alone on PRO in patients with ovarian cancer.	• Ovarian cancer specific disease/treatment-related symptoms as measured by EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L

CLINICAL STUDY REPORT SYNOPSIS

METHODS

Study Design: This was a Phase 3, multicenter, randomized, open-label, parallel 3-arm study in which approximately 550 patients who met the eligibility criteria were planned to be randomized in a 1:1:1 ratio to receive avelumab alone, avelumab in combination with pegylated liposomal doxorubicin (PLD), or PLD alone as follows:

- Arm A (Experimental, Avelumab Alone): Avelumab 10 mg/kg given as a 1-hour intravenous (IV) infusion every 2 weeks (Q2W);
- Arm B (Experimental, Avelumab + PLD): Avelumab 10 mg/kg given as a 1-hour IV Q2W + PLD 40 mg/m^2 given as a 1-hour IV infusion every 4 weeks (Q4W);
- Arm C (Control, PLD Alone): PLD 40 mg/m^2 given as a 1-hour IV infusion Q4W.

Patients were stratified by platinum-refractory or platinum-resistant status, number of prior regimens (1 versus 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) versus not. Cross-over was not permitted.

The study included up to 4 periods:

- Screening: Up to 28 days before randomization,
- Study treatment: Treatment following randomization,
- Short-term follow-up: Follow-up for 90 days after the last dose of study (hereafter referred to as follow-up),
- Long-term follow-up: Follow-up until death, End of Study, or withdrawal of consent, whichever occurred first.

Patients might have withdrawn from treatment at any time at their own request, or they might have been withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

The final analysis of this study has been completed; however, this study remains open to allow the remaining patients currently enrolled in the Arm A or Arm B to continue receiving avelumab as a single-agent or in combination with PLD. These patients will be allowed to continue receiving avelumab based on the investigator's assessment that the anticipated benefit outweighs the risks.

Diagnosis and Main Criteria for Inclusion: Eligible patients were adult patients (≥18 years of age or ≥20 years of age in Japan) with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer and who had platinum-resistant or platinum-refractory disease. Eastern Cooperative Oncology Group (ECOG) performance

CLINICAL STUDY REPORT SYNOPSIS

status was required to be 0 to 1. Patients may have received up to 3 prior lines of systemic anticancer therapy for platinum-sensitive disease, a platinum containing regimen was required as their most recent therapy and no prior systemic therapy for platinum-resistant disease was allowed. Patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 with at least 1 unidimensional measurable lesion that had not previously been irradiated.

Study Treatment: Study drugs were administered by IV infusion. In the combination arm, PLD was administered on Day 1 of each cycle and on that day it was administered first before the avelumab infusion. Refer to Table 2 for a list of study drug information involved in this study.

Table 2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
MSB0010718C solution for infusion, 20 mg/mL (10 mL/vial)	PD1F006	15-006071	200 mg	solution
MSB0010718C solution for infusion, 20 mg/mL (10 mL/vial)	PD1F011	16-000913	200 mg	solution
MSB0010718C solution for infusion, 20 mg/mL (10 mL/vial)	PD1E002	15-002315	200 mg	solution
MSB0010718C solution for infusion, 20 mg/mL (10 mL/vial)	PD1G001	16-000917	200 mg	solution
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	DCXIA1535	15-007727	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	600220P1	16-001733	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	600520P1	17-000459	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	600520P1	17-000540	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	DCXIA1559	16-002754	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10mL vial in 1x1 carton	DCXIA1557	16-002518	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10ml vial in 1x1 carton	600920P1	17-001570	2 mg/ml	commercial product
Doxorubicin HCl liposome injection 20 mg/10ml vial in 1x1 carton	HCZTK01	18-000181	2 mg/ml	commercial product
Pegylated liposomal doxorubicin HCl 20 mg/10mL vial for infusion in 1x1 carton	FAZSR00	15-005744	2 mg/ml	commercial product
Pegylated liposomal doxorubicin HCl 20 mg/10mL vial for infusion in 1x1 carton	FBZT600	15-005845	2 mg/ml	commercial product
Pegylated liposomal doxorubicin HCl 20 mg/10ml vial for infusion in 1x1 carton	FAZSR00	15-005390	2 mg/ml	commercial product
Pegylated liposomal doxorubicin HCl 20 mg/10mL vial for infusion in 1x1 carton	FEZSZ00	15-006456	2 mg/ml	commercial product

CLINICAL STUDY REPORT SYNOPSIS

Efficacy Evaluations: The primary and secondary efficacies are reported out as outlined in Table 3.

As of the data cut-off date (19 September 2018), anti-tumor activities were assessed through radiological tumor assessments conducted at baseline (screening) and every 8 weeks thereafter until documented disease progression as assessed by Blinded Independent Central Review (BICR). Radiological tumor assessments were also conducted whenever disease progression was suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 4 weeks). Complete, partial responses (CR, PR) and progressive disease were confirmed on repeated imaging ≥4 weeks after initial documentation.

The Patient Report Outcome (PRO) questionnaires were administered on the first day of each treatment cycle as well as upon End of Treatment (EOT)/Study Withdrawal and Post Treatment Safety Follow-up (Days 30, 60 and 90).

CLINICAL STUDY REPORT SYNOPSIS

Table 3. Efficacy Evaluations

Evaluation	Definition
Primary	
OS	Time from the date of randomization to the date of death due to any cause. Patients last known to be alive were censored at date of last contact.
PFS as determined by BICR	Time from randomization to the date of the first documentation of progression of disease as determined by BICR according to RECIST version 1.1, or death due to any cause, whichever occurs first. PFS data were censored on the date of the last adequate tumor assessment for patients who did not have an event (disease progression or death), for patients who started a new anti-cancer therapy prior to an event or for patients with an event after 2 or more missing tumor assessments. Patients who did not have an adequate baseline tumor assessment or who did not have an adequate post-baseline tumor assessment were censored on the date of randomization unless death occurred on or before the time of the second planned tumor assessment (ie, ≤16 weeks after the date of randomization) in which case the death was considered an event.
Secondary	
PFS as determined by investigator	Time from randomization to the date of the first documentation of progression of disease as determined by Investigator according to RECIST version 1.1 or death due to any cause, whichever occurs first. Censoring algorithm is similar to PFS based on BICR assessment.
OR based on BICR and investigator assessment	A confirmed BOR of CR or PR according to RECIST version 1.1. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met and before the first documentation of disease progression. Only tumor assessments performed on or before the start date of any further anti-cancer therapies were considered in the assessment of BOR. Patients who did not have a post-baseline radiographic tumor assessment due to early progression, who received anti-tumor therapies other than the study treatments prior to reaching a CR or PR, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of OR.
Time to Response based on BICR and investigator assessment	For patients with an OR, the time from the date of randomization to the first documentation of OR (CR or PR) which is subsequently confirmed.
DR based on BICR and investigator assessment	For patients with an OR per RECIST version 1.1, the time from the first documentation of objective tumor response (a complete or partial response) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. If a patient did not have an event (PD or death), DR was censored at the date of last adequate tumor assessment.
DC based on BICR and investigator assessment	A BOR of CR, PR, non-complete response/non-progressive disease or stable disease according to the RECIST version 1.1.

CLINICAL STUDY REPORT SYNOPSIS

Table 3 Efficacy Evaluations

Evaluation	Definition
PRO	EORTC QLQ-C30: a 30-question survey and includes 5 functional subscales (physical, role, emotional, cognitive, and social), QoL subscale, and symptom subscales/items. Higher scores on the functioning/QoL subscales indicate higher levels of functioning. Higher scores on the symptom scales/items indicate greater presence of symptoms. EORTC QLQ-OV28: a 28-item instrument with 7-symptom subscales; similar to the EORTC QLQ-C30, higher scores are reflective of a greater presence of symptoms. EQ-5D-5L: 2 components - a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); and a VAS in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable).

Biomarker Evaluations: Programmed death ligand 1 (PD-L1) expression and tumor infiltrating CD8 positive (CD8+) T lymphocytes as assessed by immunohistochemistry (IHC) were candidate predictive biomarkers in this study.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs), physical examinations, multiple-gated acquisition (MUGA)/echocardiogram, ECOG performance and safety laboratory tests.

Statistical Methods: the key statistical methods are briefly summarized as below.

Primary Efficacy

The primary analyses of Progression-Free Survival (PFS) were performed based on BICR assessment using the full analysis set (FAS), which included all randomized patients. A stratified log rank test (1-sided) stratified by randomization stratification factors was performed. PFS time was summarized by treatment arm using the Kaplan-Meier method. The Cox proportional hazards (PH) model was fitted to compute the hazard ratio and the corresponding confidence interval (CI). In order to account for the group sequential design in this study, the repeated CI (RCI) method was used to construct the 2-sided RCI for the hazard ratio. A similar analysis was performed for the primary analysis of Overall Survival (OS).

Secondary Efficacy

- Sensitivity Analyses: Sensitivity analyses were performed to explore the robustness of the primary analysis results for PFS based on BICR assessment and the primary analysis results of OS. The sensitivity analyses repeated the primary analysis (p-value, hazard ratio and 95% CIs) with modifications. PFS based on BICR assessment and OS were also analyzed based on restricted mean survival time (RMST) differences.

CLINICAL STUDY REPORT SYNOPSIS

- PFS Based on Investigator Assessment: repeated the analysis for the PFS based on investigator assessment.

- The Objective Response Rate (ORR) Based on BICR and Investigator Assessments: were estimated by dividing the number of patients with objective response (complete response [CR] or partial response [PR]) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs are provided by treatment arm. The association of treatment and Objective Response (OR) was also tested by the General Association Statistic of the Cochran-Mantel-Haenszel test (CMH) with the randomization strata taken into account.

- Time to Response Based on BICR and Investigator Assessments: are summarized using simple descriptive statistics.

- Duration of Response (DR) Based on BICR and Investigator Assessments: are summarized by treatment arm using Kaplan-Meier method. The median DR and 95% CI for the median are provided for each treatment arm.

- Disease Control Rate (DCR) Based on BICR and Investigator Assessments: defined as the proportion of patients with best overall response of CR, PR, non-complete response/non-progressive disease or stable disease (SD), was calculated for each treatment arm, along with 2-sided 95% CI using the Clopper-Pearson method.

- Subgroup Analyses: were performed for OS, PFS based on BICR assessment, OR based on BICR assessment and DR based on BICR assessment for the pre-specified subgroups.

- PRO: descriptive summaries over time are provided for the PRO endpoints. The treatment effect on time-to-deterioration (TTD) in patient's European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28 (EORTC QLQ-OV28) abdominal/gastrointestinal (GI) symptom subscale were estimated using a Cox's PH model stratified by the randomization strata to calculate the hazard ratio for the experimental arms versus control arm. Kaplan-Meier estimates (product-limit estimates) are presented by treatment arm together with a summary of associated statistics including the median TTD time with 2-sided 95% CI.

- Biomarkers: Appropriate statistical methods using biomarker analysis set was used to investigate any possible relationship of biomarker levels with avelumab anti-tumor efficacy relative to appropriate control arms.

Descriptive statistics were used to summarize all patient characteristics, treatment administration/compliance, and safety parameters. The Safety Analysis Set was the primary population for safety evaluation, which included all patients who receive at least 1 dose of study treatment (ie, avelumab or PLD).

CLINICAL STUDY REPORT SYNOPSIS

RESULTS

Subject Disposition and Demography: A total of 566 patients were randomized (188 each to the avelumab arm and the avelumab in combination with PLD arm, and 190 to the PLD arm).

Of the 566 patients randomized, 546 patients received at least 1 dose of study drug (187 in the avelumab arm, 182 in the combination arm, and 177 in the PLD arm) (Table 4). At the time of data cutoff (19 September 2018), of the 188 patients randomized to the combination treatment, 178 (94.7%) patients discontinued avelumab and 183 (97.3%) patients discontinued PLD. In the avelumab arm and the PLD arm, 182 (96.8%) and 190 (100.0%) patients discontinued from treatment, respectively (Table 4). Disease progression (progressive disease) was the primary reason for discontinuation from treatment (61.2% for avelumab and 53.7% for PLD in the combination arm, 71.8% in the avelumab arm and 49.5% in the PLD arm) (Table 4).

Patients who discontinued from treatment and did not withdraw consent continued into the follow-up phase or directly into the long-term follow-up (if the patient initiated subsequent anti-cancer therapy at the EOT or by patient request). There were 389 patients and 386 patients entering the follow-up and long-term follow-up phases, respectively. The primary reasons for discontinuation from study during follow-up and long-term follow-up were “other” (including start of new therapy) and “death”, respectively.

CLINICAL STUDY REPORT SYNOPSIS

Table 4. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Subject Disposition for Study Drugs at End of Treatment - Full Analysis Set

	Avelumab (N=188)	Avelumab + PLD (N=188)		PLD (N=190)
	Avelumab	Avelumab	PLD	PLD
	n (%)	n (%)	n (%)	n (%)
Disposition phase: end of treatment				
Discontinued	182 (96.8)	178 (94.7)	183 (97.3)	190 (100.0)
Reason for discontinuation				
Death	4 (2.1)	6 (3.2)	4 (2.1)	5 (2.6)
Progressive disease	135 (71.8)	115 (61.2)	101 (53.7)	94 (49.5)
Adverse event	16 (8.5)	29 (15.4)	37 (19.7)	21 (11.1)
Non-compliance with study drug	1 (0.5)	0	0	0
Physician decision	0	2 (1.1)	16 (8.5)	11 (5.8)
No longer meets eligibility criteria	1 (0.5)	0	0	2 (1.1)
Global deterioration of health status	19 (10.1)	19 (10.1)	19 (10.1)	24 (12.6)
Withdrawal by subject	4 (2.1)	6 (3.2)	5 (2.7)	31 (16.3)
Other	2 (1.1)	1 (0.5)	1 (0.5)	2 (1.1)
Ongoing	6 (3.2)	10 (5.3)	5 (2.7)	0

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (13:50) Source Data: ADDS Output File: ./B999_UNBLINDED/B9991009_CSR/adds_s002d Date of Generation: 25JAN2019 (17:56)
Table 14.1.1.2.4 is for Pfizer internal use.

All enrolled patients were female, and the median age was 60 years old (range 26 to 86 years). Most of the patients were from Europe (48.8%), North America (25.4%) or Asian (20.7%). Patient accrual by geographic region, country and site was similar among the 3 treatment arms. The physical measurements at baseline were similar for the 3 treatment arms. The median (range) values of Body Mass Index and body surface area (BSA) for the overall population were 25.20 (range: 14.2 to 59.8) kg/m^2 and 1.70 (range: 1.2 to 2.7) m^2, respectively.

The primary site of tumor was the ovary in the majority of patients (85.9%) followed by the peritoneum (8.7%) and the fallopian tube (5.5%). There were 251 (44.3%) patients who had a platinum-free interval of 0 to 3 months and 248 (43.8%) patients who had a platinum-free interval of >3 to 6 months.

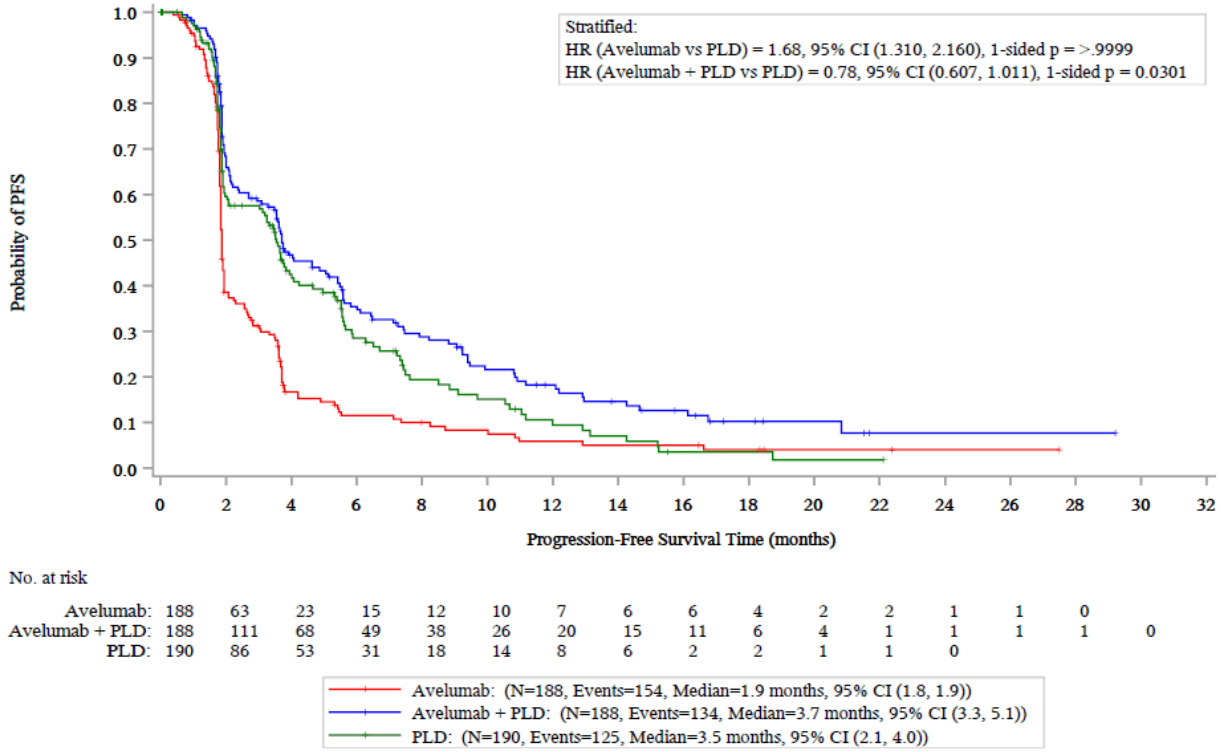
CLINICAL STUDY REPORT SYNOPSIS

Efficacy Results:

Primary – PFS Based on BICR Assessment

A Kaplan-Meier plot of PFS based on BICR is displayed in Figure 1. Median PFS based on BICR assessment was 1.9 months (95% CI: 1.8, 1.9), 3.7 months (95% CI: 3.3, 5.1) and 3.5 months (95% CI: 2.1, 4.0) for the avelumab arm, the combination arm and the PLD arm, respectively. PFS based on BICR assessment crossed the futility boundary for both avelumab versus PLD and the combination treatment versus PLD comparisons at the time of the interim analysis (IA). Updated results as of the data cutoff show a stratified hazard ratio based on 279 PFS events of 1.68 (RCI: 1.320, 2.601; 1-sided nominal p-value: >0.9999) for comparison between avelumab versus PLD, and a stratified hazard ratio based on 259 PFS events of 0.78 (RCI: 0.587, 1.244; 1-sided nominal p-value: 0.0301) for comparison between the combination treatment versus PLD.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment (RECIST v1.1) – Full Analysis Set



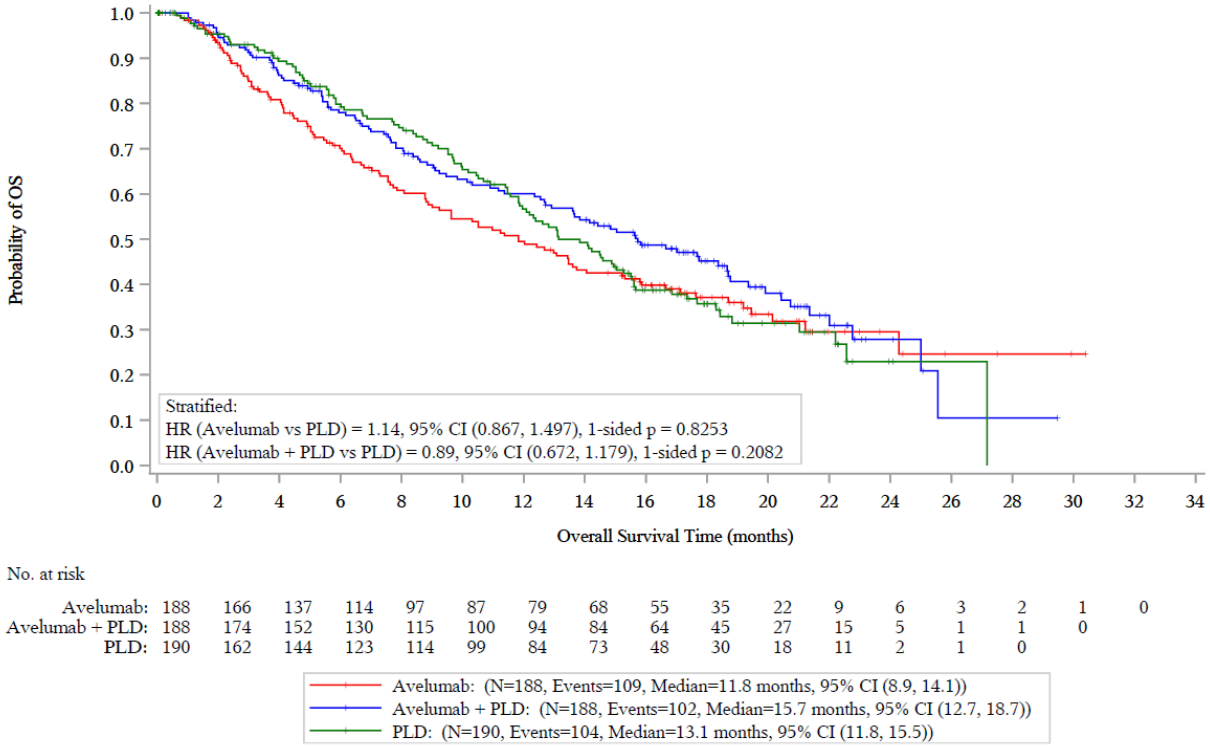
Primary – OS

A Kaplan-Meier plot of OS is displayed in Figure 2. As of the data cutoff, median OS was 11.8 months (95% CI: 8.9, 14.1), 15.7 months (95% CI: 12.7, 18.7) and 13.1 months (95% CI: 11.8, 15.5) for the avelumab arm, the combination arm and the PLD arm, respectively.

CLINICAL STUDY REPORT SYNOPSIS

OS crossed the futility boundary for the avelumab versus PLD comparison at the time of the IA. Updated results show a stratified hazard ratio (avelumab versus PLD) of 1.14 (RCI: 0.948, 1.580; 1-sided nominal p-value: 0.8253) based on the 213 deaths. The stratified hazard ratio (combination treatment versus PLD) based on 206 deaths was 0.89 (RCI: 0.744, 1.241; 1-sided p-value: 0.2082), in favor of the combination treatment. The observed p-value for the combination treatment versus PLD did not cross the threshold for statistical significance.

Figure 2. Kaplan-Meier Plot of Overall Survival - Full Analysis Set



Secondary - Sensitivity Analysis for PFS Based on BICR Assessment

The results of the sensitivity analyses were similar to those based on the primary analysis.

Secondary - Sensitivity Analysis for OS

The results of the sensitivity analyses were similar to those based on the primary analysis.

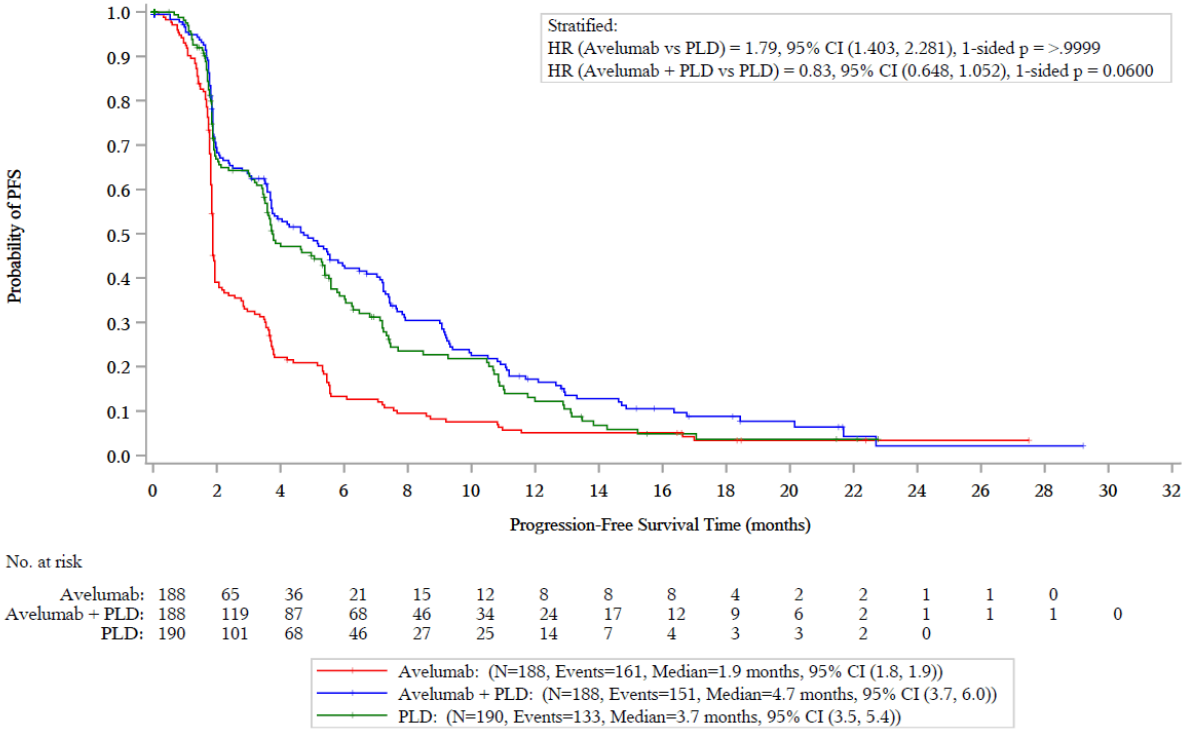
Secondary - PFS Based on Investigator Assessment

The outcome of the primary endpoint PFS based on BICR assessment was corroborated by the outcome of the secondary endpoint, PFS based on investigator assessment. Consistent with the BICR assessment, PFS based on investigator assessment was observed with a stratified hazard ratio of 1.79 (95% CI: 1.403, 2.281; 1-sided p-value>0.9999) for the comparison between avelumab versus PLD and 0.83 (95% CI: 0.648, 1.052, 1-sided

CLINICAL STUDY REPORT SYNOPSIS

p-value=0.0600) for the comparison between the combination treatment versus PLD (Figure 3).

Figure 3. Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment (RECIST v1.1) - Full Analysis Set



Secondary - Best Overall Response (BOR)

The observed ORR based on BICR assessment was 3.7% (95% CI: 1.5, 7.5) for avelumab, 13.3% (95% CI: 8.8, 19.0) for the combination treatment, and 4.2% (95% CI: 1.8, 8.1) for PLD. The stratified odds ratio was 0.890 (95% CI: 0.267, 2.901) and 3.458 (95% CI: 1.463, 9.096) for the comparison between avelumab and PLD and between the combination treatment and PLD, respectively. The proportion of patients with a BOR of confirmed CR was 0 for the avelumab and PLD arms, and 1.1% for the combination arm, whilst the proportion of patients with a BOR of progressive disease was almost half in the combination arm (31.9%) and the PLD arm (32.1%) as in the avelumab arm (53.7%).

The ORR based on investigator assessment was 5.3% (95% CI: 2.6, 9.6) for avelumab and 9.5% (95% CI: 5.7, 14.6) for PLD, and 18.6% (95% CI: 13.3, 24.9) for the combination treatment. The stratified odds ratio was 0.538 (95% CI: 0.216, 1.279) and 2.167 (95% CI: 1.145, 4.242) for the comparison between avelumab and PLD and the comparison between the combination treatment and PLD, respectively.

Secondary - Time to Response and DR

CLINICAL STUDY REPORT SYNOPSIS

For patients who had an OR as assessed by BICR, the median time to response was 2.8 months for avelumab arm, 3.6 months for the combination arm and 3.7 months for the PLD arm. The median DR as assessed by BICR for patients who responded was 9.2 months, 8.5 months and 13.1 months for the avelumab arm, the combination arm and the PLD arm, respectively.

As assessed by the investigator, for patients who had an OR, the median time to response was 1.9 months for the avelumab arm, 3.7 months for the combination arm and 3.5 months for the PLD arm.

Secondary - DCR

The DCR for the avelumab arm, the combination arm and the PLD arm was 33.0%, 57.4% and 48.9%, respectively, based on the BICR assessment; and was 34.0%, 61.7% and 54.7%, respectively, based on the investigator assessment.

Secondary - Patient-Reported Outcomes

The median TTD for EORTC QLQ-OV28 (the abdominal/GI subscale) was not estimable for the avelumab arm, 11.1 months for the combination arm and 10.6 months for the PLD arm. The hazard ratio (95% CI) was 1.41 (0.863, 2.306) for avelumab versus PLD and 1.24 (0.790, 1.934) for the combination treatment versus PLD.

Biomarker Results

Of the total population evaluable for the PD-L1 biomarker analysis, 57% had PD-L1 positive (PD-L1+) tumors; and the proportion of patients with PD-L1+ tumors of each treatment arm was similar.

Within the combination arm, the median value of PFS based on BICR was slightly higher in the PD-L1+ subgroup as compared to the PD-L1- subgroup. The unstratified hazard ratio with respect to PFS based on BICR assessment in the PD-L1+ subgroup as compared to the PD-L1 negative (PD-L1-) subgroup was 0.95 within the avelumab arm, 0.71 within the combination arm and 1.16 within the PLD arm. The hazard ratios with respect to PFS in the PD-L1- subgroup were greater than 1 for both the avelumab alone and combination arms when compared to the PLD arm. The hazard ratios in the PD-L1+ subgroup were 1.45 for avelumab versus PLD and 0.65 for the combination treatment versus PLD.

Within the combination arm, the median value of OS was higher in the PD-L1+ subgroup as compared to the PD-L1- subgroup. The unstratified hazard ratio with respect to OS in the PD-L1+ subgroup as compared to the PD-L1- subgroup was 0.62 within the avelumab arm, 0.65 within the combination arm and 0.99 within the PLD arm. The hazard ratios with respect to OS in the PD-L1- subgroup were greater than 1 for both the avelumab and the combination arms when compared to the PLD arm. The hazard ratios in the PD-L1+ subgroup were 0.83 for the avelumab arm versus the PLD arm, and 0.72 for the combination arm versus the PLD arm.

CLINICAL STUDY REPORT SYNOPSIS

Of the total population evaluable for the CD8 T cell biomarker analysis, 46% patients had CD8+ tumors; and the proportion of patients with CD8+ tumors of each treatment arm was similar.

Within the combination arm, the median value of PFS based on BICR was higher in the CD8+ subgroup as compared to the CD8 negative (CD8-) subgroup. The unstratified hazard ratio with respect to PFS based on BICR assessment in the CD8+ subgroup as compared to the CD8- subgroup was 0.93 within the avelumab arm, 0.69 within the combination arm and 0.95 within the PLD arm. Hazard ratios with respect to PFS in the CD8- subgroup were 1.53 and 0.92 for the avelumab arm and the combination arm respectively when compared to the PLD arm. The hazard ratios in the CD8+ subgroup were 1.58 for the avelumab arm versus the PLD arm, and 0.64 for the combination arm versus the PLD arm.

Within the combination arm, the median value of OS was higher in the CD8+ subgroup as compared to the CD8- subgroup. The unstratified hazard ratio with respect to OS in the CD8+ subgroup as compared to the CD8- subgroup was 0.89 within the avelumab arm, 0.62 within the combination arm and 0.88 within the PLD arm. Hazard ratios with respect to OS in the CD8- subgroup were 1.01 and 0.97 for the avelumab arm and the combination arm respectively when compared to the PLD. The hazard ratios in the CD8+ subgroup were 1.03 for the avelumab arm versus the PLD arm, and 0.66 for the combination arm versus the combination arm.

Safety Results:
An overview of the treatment-emergent adverse events (TEAEs) is provided in Table 5. The proportions of patients with TEAEs were similar among the treatment arms (96.3%, 98.8% and 97.7% for avelumab, combination treatment and PLD, respectively). However the combination treatment arm had a higher proportion of patients with treatment-related TEAEs, grade ≥3 TEAEs or TEAEs leading to discontinuation from any study drug. The treatment-emergent serious adverse event (SAE) incidence was higher in avelumab treated patients (avelumab alone [38.0%] and in combination [41.2%]), compared with the PLD arm (28.8%).

CLINICAL STUDY REPORT SYNOPSIS

Table 5. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of Adverse Events During the On-Treatment Period - Safety Analysis Set

Number (%) of Subjects	Avelumab (N=187) n (%)	Avelumab + PLD (N=182) n (%)	PLD (N=177) n (%)
Subjects with TEAEs	180 (96.3)	180 (98.9)	173 (97.7)
Subjects with grade ≥ 3 TEAEs	93 (49.7)	125 (68.7)	105 (59.3)
Subjects with treatment-related TEAEs	135 (72.2)	168 (92.3)	151 (85.3)
Subjects with grade ≥ 3 treatment-related TEAEs	30 (16.0)	78 (42.9)	56 (31.6)
Subjects with serious TEAEs	71 (38.0)	75 (41.2)	51 (28.8)
Subjects with serious treatment-related TEAEs	14 (7.5)	32 (17.6)	19 (10.7)
Subjects with TEAEs leading to dose reduction of Avelumab	0	0	0
Subjects with TEAEs leading to dose reduction of PLD	0	39 (21.4)	23 (13.0)
Subjects with TEAEs leading to interruption of Avelumab	48 (25.7)	113 (62.1)	0
Subjects with TEAEs leading to interruption of PLD	0	79 (43.4)	57 (32.2)
Subjects with TEAEs leading to discontinuation of Avelumab	19 (10.2)	32 (17.6)	0
Subjects with TEAEs leading to discontinuation of PLD	0	37 (20.3)	18 (10.2)
Subjects with TEAEs leading to discontinuation of any study drug	19 (10.2)	48 (26.4)	18 (10.2)
Subjects with TEAEs leading to discontinuation of all study drugs	19 (10.2)	15 (8.2)	18 (10.2)
Subjects with treatment-related TEAEs leading to discontinuation of Avelumab	12 (6.4)	22 (12.1)	0
Subjects with treatment-related TEAEs leading to discontinuation of PLD	0	30 (16.5)	13 (7.3)
Subjects with treatment-related TEAEs leading to discontinuation of any study drug	12 (6.4)	38 (20.9)	13 (7.3)
Subjects with treatment-related TEAEs leading to discontinuation of all study drugs	12 (6.4)	8 (4.4)	13 (7.3)
Subjects with TEAEs leading to death	15 (8.0)	8 (4.4)	6 (3.4)
Subjects with treatment-related TEAEs leading to death	1 (0.5)	0	1 (0.6)
Subjects with immune-related adverse events (irAEs)	25 (13.4)	51 (28.0)	8 (4.5)
Subjects with infusion-related reactions (IRRs)	38 (20.3)	30 (16.5)	17 (9.6)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
For combination arm, treatment-related AEs include AEs related to at least one study drug in the combination.
Any study drug = at least one study drug in the combination. All study drugs = all study drugs in the combination.
AEs leading to Interruption are AEs with action taken with study treatment of 'Drug interrupted' in CRF but excluding IRRs that only lead to interruption of the
infusion.
MedDRA (v21.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAE Output File: ./B999_UNBLINDED/B9991009_CSR/adae_s020 Date of Generation: 26JAN2019 (08:53)
Table 14.3.1.2.1 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

The TEAE incidences are summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and maximum Common Terminology Criteria for Adverse Events (CTCAE) grade. The incidences of TEAEs with any grade in ≥10% and grade ≥3 in ≥5% patients are presented in Table 6 (all-causality) and Table 7 (treatment-related).

More than half of the 533 patients with any TEAEs experienced TEAEs of grade ≥3 (Table 6). Avelumab treated patients had higher incidences of Grade 5 TEAEs (8.0% and 4.4% compared with 3.4% on PLD), most of which were coded as Disease progression PT. The most frequent all-causality TEAEs in the combination arm (≥30% patients) were Fatigue, Nausea, Anaemia and Palmar-plantar erythrodysaesthesia syndrome (Table 6). The most frequent treatment-related TEAEs in the combination arm (≥30% patients) were Fatigue, Nausea, and Palmar-plantar erythrodysaesthesia syndrome (Table 7).

CLINICAL STUDY REPORT SYNOPSIS

Table 6. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of Most Common TEAEs (Any Grade in ⩾ 10% Subjects or Grade ⩾3 in ⩾5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Avelumab (N=187)		Avelumab + PLD (N=182)		PLD (N=177)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	180 (96.3)	93 (49.7)	180 (98.9)	125 (68.7)	173 (97.7)	105 (59.3)
Fatigue	63 (33.7)	4 (2.1)	77 (42.3)	14 (7.7)	55 (31.1)	8 (4.5)
Abdominal pain	57 (30.5)	14 (7.5)	48 (26.4)	13 (7.1)	41 (23.2)	10 (5.6)
Nausea	57 (30.5)	7 (3.7)	89 (48.9)	9 (4.9)	77 (43.5)	2 (1.1)
Vomiting	47 (25.1)	7 (3.7)	44 (24.2)	5 (2.7)	45 (25.4)	4 (2.3)
Diarrhoea	43 (23.0)	9 (4.8)	37 (20.3)	2 (1.1)	32 (18.1)	4 (2.3)
Decreased appetite	38 (20.3)	4 (2.1)	51 (28.0)	4 (2.2)	37 (20.9)	1 (0.6)
Constipation	37 (19.8)	2 (1.1)	48 (26.4)	3 (1.6)	45 (25.4)	1 (0.6)
Dyspnoea	36 (19.3)	8 (4.3)	33 (18.1)	4 (2.2)	25 (14.1)	2 (1.1)
Anaemia	32 (17.1)	9 (4.8)	55 (30.2)	12 (6.6)	42 (23.7)	16 (9.0)
Pyrexia	32 (17.1)	1 (0.5)	37 (20.3)	2 (1.1)	17 (9.6)	1 (0.6)
Back pain	22 (11.8)	2 (1.1)	17 (9.3)	3 (1.6)	23 (13.0)	4 (2.3)
Chills	19 (10.2)	0	14 (7.7)	0	3 (1.7)	0
Asthenia	18 (9.6)	1 (0.5)	30 (16.5)	8 (4.4)	14 (7.9)	1 (0.6)
Cough	17 (9.1)	0	28 (15.4)	0	24 (13.6)	0
Abdominal distension	15 (8.0)	5 (2.7)	18 (9.9)	1 (0.5)	18 (10.2)	1 (0.6)
Headache	15 (8.0)	0	27 (14.8)	0	11 (6.2)	0
Intestinal obstruction	15 (8.0)	15 (8.0)	13 (7.1)	8 (4.4)	6 (3.4)	6 (3.4)
Urinary tract infection	15 (8.0)	3 (1.6)	20 (11.0)	1 (0.5)	14 (7.9)	4 (2.3)
Infusion related reaction	13 (7.0)	0	19 (10.4)	1 (0.5)	16 (9.0)	1 (0.6)
Oedema peripheral	13 (7.0)	2 (1.1)	25 (13.7)	1 (0.5)	14 (7.9)	0
Pruritus	13 (7.0)	0	21 (11.5)	0	8 (4.5)	0
Rash	11 (5.9)	0	51 (28.0)	11 (6.0)	19 (10.7)	3 (1.7)
Hypothyroidism	8 (4.3)	0	19 (10.4)	0	2 (1.1)	0
Stomatitis	8 (4.3)	1 (0.5)	53 (29.1)	10 (5.5)	36 (20.3)	5 (2.8)
Dry skin	5 (2.7)	0	22 (12.1)	0	8 (4.5)	1 (0.6)
Mucosal inflammation	4 (2.1)	1 (0.5)	25 (13.7)	3 (1.6)	19 (10.7)	3 (1.7)
Neutropenia	1 (0.5)	1 (0.5)	26 (14.3)	10 (5.5)	26 (14.7)	9 (5.1)

CLINICAL STUDY REPORT SYNOPSIS

Table 6. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of Most Common TEAEs (Any Grade in ⩾ 10% Subjects or Grade ⩾3 in ⩾5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Avelumab (N=187)		Avelumab + PLD (N=182)		PLD (N=177)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.5)	0	61 (33.5)	18 (9.9)	40 (22.6)	9 (5.1)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
MedDRA (v21.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAE Output File: ./B999_UNBLINDED/B9991009_CSR/adae_s999a Date of Generation: 26JAN2019 (09:00)
Table 14.3.1.2.6 is for Pfizer internal use.

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Table 7. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of Most Common Treatment-related TEAEs (Any Grade in ⩾10% Subjects or Grade ⩾3 in ⩾5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Avelumab (N=187)		Avelumab + PLD (N=182)		PLD (N=177)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	135 (72.2)	30 (16.0)	168 (92.3)	78 (42.9)	151 (85.3)	56 (31.6)
Fatigue	42 (22.5)	0	60 (33.0)	10 (5.5)	42 (23.7)	3 (1.7)
Nausea	25 (13.4)	0	65 (35.7)	3 (1.6)	64 (36.2)	1 (0.6)
Diarrhoea	24 (12.8)	5 (2.7)	19 (10.4)	1 (0.5)	20 (11.3)	0
Pyrexia	21 (11.2)	0	22 (12.1)	0	5 (2.8)	0
Anaemia	19 (10.2)	3 (1.6)	39 (21.4)	6 (3.3)	34 (19.2)	9 (5.1)
Vomiting	16 (8.6)	1 (0.5)	21 (11.5)	1 (0.5)	28 (15.8)	3 (1.7)
Infusion related reaction	13 (7.0)	0	19 (10.4)	1 (0.5)	14 (7.9)	1 (0.6)
Decreased appetite	11 (5.9)	0	33 (18.1)	1 (0.5)	26 (14.7)	0
Rash	9 (4.8)	0	45 (24.7)	11 (6.0)	16 (9.0)	3 (1.7)
Asthenia	8 (4.3)	0	21 (11.5)	4 (2.2)	9 (5.1)	1 (0.6)
Pruritus	7 (3.7)	0	19 (10.4)	0	6 (3.4)	0
Mucosal inflammation	4 (2.1)	1 (0.5)	24 (13.2)	3 (1.6)	17 (9.6)	3 (1.7)
Stomatitis	4 (2.1)	0	51 (28.0)	10 (5.5)	36 (20.3)	5 (2.8)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.5)	0	60 (33.0)	18 (9.9)	40 (22.6)	9 (5.1)
Neutropenia	0	0	24 (13.2)	9 (4.9)	26 (14.7)	9 (5.1)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
For combination arm, treatment-related AEs include AEs related to at least one study drug in the combination.
MedDRA (v21.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAE Output File: ./B999_UNBLINDED/B9991009_CSR/adae_s999b Date of Generation: 26JAN2019 (09:38)
Table 14.3.1.3.1.1 is for Pfizer internal use.

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A summary for all-grade and grade ≥3 immune-related AE (irAE) incidences are presented in Table 8. As expected based on avelumab's mechanism of action, the proportion of patients with irAEs was higher in the avelumab arm and in the combination arm than in the PLD arm (13.4% and 28.0% versus 4.5% for all grades, 3.7% and 8.2% versus 0.6% for grade ≥3). The most common irAE categories were "Immune-related Endocrinopathies: Thyroid Disorders" (5.9%, 9.9% and 1.1% in the avelumab arm, the combination arm and the PLD arm, respectively) and "Immune-related Rash" (3.2%, 18.1% and 3.4% in the avelumab arm, the combination arm and the PLD arm, respectively).

Table 8. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of irAEs by Cluster, PT and Maximum CTCAE Grade - Safety Analysis Set

	Avelumab (N=187)		Avelumab + PLD (N=182)		PLD (N=177)	
	All Grades	Grade≥3	All Grades	Grade≥3	All Grades	Grade≥3
Cluster and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with events	25 (13.4)	7 (3.7)	51 (28.0)	15 (8.2)	8 (4.5)	1 (0.6)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	11 (5.9)	1 (0.5)	18 (9.9)	0	2 (1.1)	0
Hypothyroidism	7 (3.7)	0	17 (9.3)	0	2 (1.1)	0
Hyperthyroidism	5 (2.7)	1 (0.5)	3 (1.6)	0	0	0
Autoimmune thyroiditis	0	0	1 (0.5)	0	0	0
Basedow's disease	0	0	1 (0.5)	0	0	0
IMMUNE-RELATED RASH	6 (3.2)	1 (0.5)	33 (18.1)	12 (6.6)	6 (3.4)	1 (0.6)
Rash	4 (2.1)	0	20 (11.0)	7 (3.8)	2 (1.1)	0
Rash erythematous	1 (0.5)	1 (0.5)	1 (0.5)	0	0	0
Rash macular	1 (0.5)	0	1 (0.5)	0	1 (0.6)	0
Rash maculo-papular	1 (0.5)	0	7 (3.8)	4 (2.2)	1 (0.6)	0
Dermatitis exfoliative generalised	0	0	0	0	1 (0.6)	1 (0.6)
Drug eruption	0	0	1 (0.5)	0	0	0
Erythema	0	0	1 (0.5)	0	0	0
Pruritus	0	0	4 (2.2)	0	0	0
Rash papular	0	0	1 (0.5)	0	0	0
Rash pruritic	0	0	2 (1.1)	1 (0.5)	1 (0.6)	0
Skin toxicity	0	0	2 (1.1)	0	0	0
Toxic skin eruption	0	0	1 (0.5)	0	0	0
IMMUNE-RELATED HEPATITIS	4 (2.1)	3 (1.6)	1 (0.5)	1 (0.5)	0	0
Alanine aminotransferase increased	2 (1.1)	1 (0.5)	1 (0.5)	1 (0.5)	0	0
Aspartate aminotransferase increased	2 (1.1)	2 (1.1)	0	0	0	0

CLINICAL STUDY REPORT SYNOPSIS

Table 8. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of irAEs by Cluster, PT and Maximum CTCAE Grade - Safety Analysis Set

	Avelumab (N=187)		Avelumab + PLD (N=182)		PLD (N=177)	
	All Grades	Grade≥3	All Grades	Grade≥3	All Grades	Grade≥3
Cluster and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Autoimmune hepatitis	1 (0.5)	1 (0.5)	0	0	0	0
Drug-induced liver injury	1 (0.5)	1 (0.5)	0	0	0	0
Hepatitis	1 (0.5)	0	0	0	0	0
IMMUNE-RELATED PNEUMONITIS	4 (2.1)	1 (0.5)	3 (1.6)	0	0	0
Pneumonitis	4 (2.1)	1 (0.5)	3 (1.6)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS	2 (1.1)	0	0	0	0	0
Rheumatoid arthritis	1 (0.5)	0	0	0	0	0
Sjogren's syndrome	1 (0.5)	0	0	0	0	0
IMMUNE-RELATED COLITIS	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0	0
Diarrhoea	1 (0.5)	1 (0.5)	0	0	0	0
Colitis	0	0	1 (0.5)	1 (0.5)	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	0	0	2 (1.1)	1 (0.5)	0	0
Adrenal insufficiency	0	0	2 (1.1)	1 (0.5)	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: PITUITARY DYSFUNCTION	0	0	2 (1.1)	1 (0.5)	0	0
Hypopituitarism	0	0	2 (1.1)	1 (0.5)	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same cluster are counted only once within each cluster.
For subjects reporting more than one AE within a cluster or preferred term, the AE with maximum grade is included in the table.
MedDRA (v21.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAEI Output File: ./B999_UNBLINDED/B9991009_CSR/adae_s062_irae3 Date of Generation: 26JAN2019 (09:44)
Table 14.3.3.3.1.1.1.1 is for Pfizer internal use.

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A summary for infusion-related reactions (IRR) incidences are presented in Table 9. There were 38 (20.3%), 30 (16.5%) and 17 (9.6%) patients that experienced a TEAE that met the case definition of an IRR in the avelumab, combination and PLD arms, respectively. The most commonly reported IRR PT was Infusion related reaction, experienced by 13 (7.0%) patients in the avelumab arm, 11 (6.0%) patients in the combination arm and 14 (7.9%) patients in the PLD arm.

Table 9. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of IRRs - Safety Analysis Set

	Avelumab (N=187) n (%)	Avelumab + PLD (N=182) n (%)	PLD (N=177) n (%)
Subjects with IRR	38 (20.3)	30 (16.5)	17 (9.6)
Chills	13 (7.0)	11 (6.0)	0
Infusion related reaction	13 (7.0)	11 (6.0)	14 (7.9)
Pyrexia	12 (6.4)	10 (5.5)	1 (0.6)
Abdominal pain	1 (0.5)	0	1 (0.6)
Drug hypersensitivity	1 (0.5)	1 (0.5)	0
Flushing	1 (0.5)	0	2 (1.1)
Hypersensitivity	1 (0.5)	1 (0.5)	1 (0.6)
Hypotension	1 (0.5)	0	0
Anaphylactic reaction	0	0	1 (0.6)
Back pain	0	1 (0.5)	0
Dyspnoea	0	0	1 (0.6)
Urticaria	0	0	2 (1.1)
Wheezing	0	0	1 (0.6)
Subjects with IRR (maximum severity)			
Grade 1	24 (12.8)	14 (7.7)	3 (1.7)
Grade 2	14 (7.5)	15 (8.2)	12 (6.8)
Grade 3	0	1 (0.5)	1 (0.6)
Grade 4	0	0	1 (0.6)
Grade 5	0	0	0
Grade ≥ 3	0	1 (0.5)	2 (1.1)
Subjects with IRR leading to discontinuation	2 (1.1)	1 (0.5)	2 (1.1)
Subjects with serious IRR	5 (2.7)	6 (3.3)	2 (1.1)

CLINICAL STUDY REPORT SYNOPSIS

Table 9. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of IRRs - Safety Analysis Set

	Avelumab (N=187)	Avelumab + PLD (N=182)	PLD (N=177)
	n (%)	n (%)	n (%)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term are counted only once in that preferred term.
MedDRA (v21.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAE Output File: ./B999_UNBLINDED/B9991009_CSR/adae_irr_s Date of Generation: 26JAN2019 (10:01)
Table 14.3.3.3.2.1.3 is for Pfizer internal use.

There was a higher proportion of patients in the combination arm with TEAEs leading to permanent discontinuation of either study drug compared with avelumab and PLD (26.4% versus 10.2% and 10.2%, respectively). The proportion of patients who discontinued both study drugs was similar across treatment arms (8.2% versus 10.2% and 10.2% patients, respectively). The most common TEAE leading to the discontinuation of avelumab was Intestinal obstruction (1.6% and 0.5% patients on avelumab and on the combination treatment, respectively). The most common TEAE leading to the discontinuation of PLD was Palmar-plantar erythrodysaesthesia syndrome (4.4% and 1.7% patients in the combination treatment and PLD arms, respectively).

CLINICAL STUDY REPORT SYNOPSIS

As of the data cutoff, 57.8% patients in the avelumab arm, 53.8% patients in the combination arm, and 58.2% patients in the PLD arm had died. The primary reason for death was disease progression (48.7% patients in the avelumab arm, 50.5% patients in the combination arm and 50.8 % patients in the PLD arm). TEAEs leading to death are summarized by system organ class (SOC) and PT in Table 10.

Table 10. MSB0010718C Protocol B9991009 - (Cutoff date: 19SEP2018, Snapshot Date: 29OCT2018) Summary of TEAEs During the On-Treatment Period Leading to Death by SOC and PT - Safety Analysis Set

System Organ Class and Preferred Term	Avelumab (N=187) n (%)	Avelumab + PLD (N=182) n (%)	PLD (N=177) n (%)
Subjects with events	15 (8.0)	8 (4.4)	6 (3.4)
General disorders and administration site conditions	11 (5.9)	6 (3.3)	2 (1.1)
Disease progression	9 (4.8)	5 (2.7)	2 (1.1)
General physical health deterioration	2 (1.1)	1 (0.5)	0
Gastrointestinal disorders	3 (1.6)	0	1 (0.6)
Intestinal obstruction	3 (1.6)	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0	2 (1.1)
Pneumonia aspiration	1 (0.5)	0	0
Lung disorder	0	0	1 (0.6)
Pulmonary embolism	0	0	1 (0.6)
Infections and infestations	0	1 (0.5)	1 (0.6)
Meningitis	0	1 (0.5)	0
Sepsis	0	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5)	0
Malignant neoplasm progression	0	1 (0.5)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same system organ class (SOC) are counted only once within each SOC.
MedDRA (v21.0) coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30OCT2018 (17:50) Source Data: ADAE Output File: ./B999_UNBLINDED/B9991009_CSR/adae_s050 Date of Generation: 26JAN2019 (08:55)
Table 14.3.1.2.4 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

The most common serious TEAEs were Intestinal obstruction and Abdominal pain. The most common treatment-related serious TEAE was Pyrexia, reported in the avelumab arm and in the combination arm.

Overall, there was a higher proportion of liver function test (LFT) abnormalities in the combination arm. None of the abnormalities met the criteria for a potential Hy's Law case.

The proportions of patients with the QT interval corrected using Fridericia's Formula (QTcF) >500 msec or QTcF changes from baseline >60 msec were small and similar among the 3 treatment arms. One [1 (0.8%)], 1 (0.6%) and 2 (1.5%) patients, respectively, had a Left Ventricular Ejection Fraction (LVEF)% ≥15 points decrease from baseline to a post baseline value <lower limit of normal (LLN); and 1 (0.8%), 3 (1.9%), and 2 (1.5%) patients, respectively, had a LVEF% ≥10 points decrease from baseline to a post baseline value <LLN.

Conclusions:

- Avelumab, administered alone or in combination with PLD, was not superior to PLD monotherapy in prolonging PFS (as assessed by BICR) or OS, in the treatment of patients with platinum resistant/refractory ovarian cancer.

- The observed ORR based on BICR assessment was higher for avelumab administered in combination with PLD and similar for avelumab alone compared with that for PLD alone.

- The results of the analyses for tumor-related efficacy endpoints based on investigator assessment were similar to those based on BICR assessment.

- PFS and OS were extended following treatment with avelumab in combination with PLD compared to PLD alone in patients whose tumors expressed PD-L1 and in those containing CD8+ T-cells, when compared to patients whose tumors did not express these markers. These data, while not conclusive in the context of this study, indicate that PD-L1 expression or the presence of CD8 T-cells have potential as predictive biomarkers for the activity of avelumab in combination with PLD in this patient population.

- The observed TTD results, as measured by the abdominal/GI subscale of the EORTC QLQ-OV28 were similar for avelumab, either alone or in combination, compare to PLD alone.

- The safety profile of avelumab, administered alone or in combination with PLD, was generally tolerable, manageable, and consistent with the known safety profiles of avelumab and PLD when administered as monotherapies.